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JAMA Internal Medicine | Original Investigation

Clinical Effectiveness and Safety of Aspirin for Venous Thromboembolism Prophylaxis After Total Hip and Knee Replacement

A Systematic Review and Meta-analysis of Randomized Clinical Trials

Gulraj S. Matharu, DPhil; Setor K. Kunutsor, PhD; Andrew Judge, PhD; Ashley W. Blom, PhD; Michael R. Whitehouse, PhD

IMPORTANCE Patients undergoing total hip replacement (THR) and total knee replacement (TKR) receive venous thromboembolism (VTE) pharmacoprophylaxis. It is unclear which anticoagulant is preferable. Observational data suggest aspirin provides effective VTE prophylaxis.

OBJECTIVE To assess the effectiveness and safety of aspirin for VTE prophylaxis after THR and TKR.

DATA SOURCES A systematic review and meta-analysis was performed of randomized clinical trials (RCTs), with no language restrictions, from inception to September 19, 2019, using MEDLINE, Embase, Web of Science, Cochrane Library, and bibliographic searches. The computer-based searches combined terms and combinations of keywords related to the population (eg, *hip replacement*, *knee replacement*, *hip arthroplasty*, and *knee arthroplasty*), drug intervention (eg, *aspirin*, *heparin*, *clexane*, *dabigatran*, *rivaroxaban*, and *warfarin*), and outcome (eg, *venous thromboembolism*, *deep vein thrombosis*, *pulmonary embolism*, and *bleeding*) in humans.

STUDY SELECTION This study included RCTs assessing the effectiveness and safety of aspirin for VTE prophylaxis compared with other anticoagulants in adults undergoing THR and TKR. The RCTs with a placebo control group were excluded. The searches and study selection were independently performed.

DATA EXTRACTION AND SYNTHESIS This study followed PRISMA recommendations and used the Cochrane Collaboration's risk of bias tool. Data were screened and extracted independently by both reviewers. Study-specific relative risks (RRs) were aggregated using random-effects models. Quality of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

MAIN OUTCOMES AND MEASURES The primary outcome was any postoperative VTE (asymptomatic or symptomatic). Secondary outcomes were adverse events associated with therapy, including bleeding.

RESULTS Of 437 identified articles, 13 RCTs were included (6060 participants; 3466 [57.2%] women; mean age, 63.0 years). The RR of VTE after THR and TKR was 1.12 (95% CI, 0.78-1.62) for aspirin compared with other anticoagulants. Comparable findings were observed for deep vein thrombosis (DVT) (RR, 1.04; 95% CI, 0.72-1.51) and pulmonary embolism (PE) (RR, 1.01; 95% CI, 0.68-1.48). The risk of adverse events, including major bleeding, wound hematoma, and wound infection, was not statistically significantly different in patients receiving aspirin vs other anticoagulants. When analyzing THRs and TKRs separately, there was no statistically significant difference in the risk of VTE, DVT, and PE between aspirin and other anticoagulants. Aspirin had a VTE risk not statistically significantly different from low-molecular-weight heparin (RR, 0.76; 95% CI, 0.37-1.56) or rivaroxaban (RR, 1.52; 95% CI, 0.56-4.12). The quality of the evidence ranged from low to high.

CONCLUSIONS AND RELEVANCE In terms of clinical effectiveness and safety profile, aspirin did not differ statistically significantly from other anticoagulants used for VTE prophylaxis after THR and TKR. Future trials should focus on noninferiority analysis of aspirin compared with alternative anticoagulants and cost-effectiveness.

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Total hip replacement (THR) and total knee replacement (TKR) are common and effective interventions for degenerative joint conditions, such as osteoarthritis.[1] Venous thromboembolism (VTE) (deep vein thrombosis [DVT] and pulmonary embolism [PE]) is an important cause of long-term morbidity, represents a preventable cause of mortality, and has substantial health care costs.[2] All patients undergoing joint replacement are at risk of VTE because of the duration of surgery and reduced perioperative mobility. To reduce VTE risk, almost all patients receive up to 35 days of anticoagulation after surgery.[3] Rates of VTE at 90 days after THR and TKR are variable (up to 5% for DVT and up to 2% for PE in anticoagulated patients).[4]

Anticoagulants for preventing VTE include simple oral agents (aspirin), injectable agents (low-molecular-weight heparin [LMWH]), and newer oral agents (dabigatran etexilate and rivaroxaban). Aspirin is inexpensive, is easily administered, requires no blood monitoring, and is well tolerated, with an excellent safety profile.[5] Currently, aspirin is used off-label for VTE prevention in both the United States and the United Kingdom. However, there are some concerns that the newer and more expensive oral agents may have higher bleeding risks, including major hemorrhage and wound problems.[5] Therefore, considerable debate remains about which agents should be preferred given that clinical effectiveness must be balanced against bleeding risk and cost.

Major efforts have been made by organizations to produce guidelines for preventing VTE that use a rigorous approach to evidence synthesis and formulating recommendations. These organizations include the American Academy of Orthopaedic Surgeons (AAOS), the American College of Chest Physicians (ACCP), and the UK National Institute for Health and Care Excellence (NICE).[6-8] The 2011 AAOS guideline, which was based on a moderate level of evidence, recommended that patients undergoing THR or TKR should receive VTE prophylaxis (pharmacologic and/or mechanical).[6] However, at that time, the AAOS was unable to recommend for or against any specific VTE prophylactic agents because of a lack of evidence.[6] In 2012, the ACCP endorsed aspirin for VTE prophylaxis after THR and TKR, with a grade of 1B (moderate evidence) compared with no VTE prophylaxis, which is the same level of evidence assigned to both injectable and newer oral agents compared with no VTE prophylaxis.[7] In 2018, the NICE recommended aspirin alone as an option for VTE prophylaxis after TKR; however, after THR, patients require 10 days of LMWH before receiving aspirin, or they may solely receive the newer, more expensive oral agents or LMWH.[8]

Although observational data provide some support for aspirin as VTE prophylaxis after THR and TKR, good-quality randomized clinical trials (RCTs) supporting aspirin use are limited.[4,5] However, a large RCT (n = 3424), not included in the latest recommendations from the AAOS, ACCP, or NICE was recently published[9] in which all patients received 5 days of rivaroxaban after THR and TKR before being randomized to continue rivaroxaban or switch to aspirin.[6-9] Given that this trial[9] has not been considered in any previous meta-analysis to date, it may change the interpretation of existing data. We assessed the clinical effectiveness and safety of aspirin compared with other anticoagulants for VTE prophylaxis after THR and TKR by performing a systematic review and meta-analysis of RCTs.

Key Points

Question What is the effectiveness and safety of aspirin for venous thromboembolism prophylaxis after total hip and knee replacement?

Findings In this systematic review and meta-analysis of 13 randomized clinical trials (6060 participants), the risk of venous thromboembolism after total hip and knee replacement was not statistically significantly different when using aspirin compared with other anticoagulants. Adverse events, including major bleeding, wound hematoma, and infection, were not statistically significantly different in patients receiving aspirin compared with other anticoagulants.

Meaning The effectiveness and safety of aspirin did not appear to have been statistically significantly different from other anticoagulants used for venous thromboembolism prophylaxis after total hip and knee replacement and hence remains an option for use.

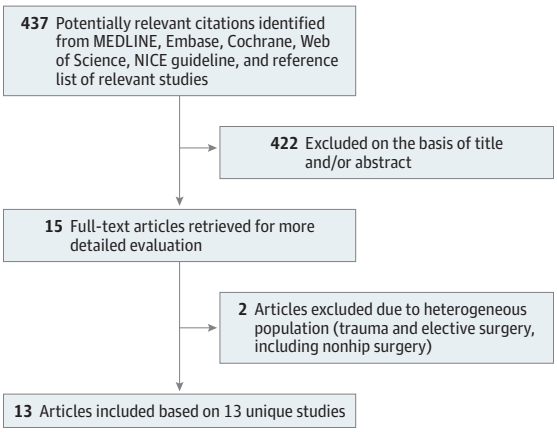
Methods

Search Strategy and Selection Criteria

We performed a systematic review and meta-analysis of RCTs using a predefined protocol as per the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations.[10] Two of us (G.S.M. and S.K.K.) independently searched MEDLINE, Embase, Web of Science, and Cochrane Library databases for relevant articles (from inception to September 19, 2019). The computer-based searches combined terms and combinations of keywords related to the population (eg, *hip replacement*, *knee replacement*, *hip arthroplasty*, and *knee arthroplasty*), drug intervention (eg, *aspirin*, *heparin*, *clexane*, *dabigatran*, *rivaroxaban*, and *warfarin*), and outcome (eg, *venous thromboembolism*, *deep vein thrombosis*, *pulmonary embolism*, and *bleeding*) in humans, with no language restrictions. All trials included in the recent NICE VTE prevention guideline were also assessed for suitability.[8] The search strategy and specific terms used are listed in eTable 1 in the Supplement. Two of us (G.S.M. and S.K.K.) independently screened titles and abstracts of all initially identified studies according to the selection criteria. Full-text articles of studies meeting the selection criteria were retrieved. Reference lists of selected studies and relevant review articles were manually searched for relevant articles.

We included RCTs assessing the clinical effectiveness and safety of aspirin for VTE prophylaxis compared with other agents in adults (≥18 years) undergoing THR or TKR. Patients had to be randomized to aspirin or another anticoagulant for inclusion. Trials using hybrid VTE prophylaxis strategies in which aspirin was 1 of 2 agents used (eg, an initial course of LMWH before a longer course of aspirin) were included to reflect current practice.[8,9,11] We excluded all other study types (nonrandomized and observational studies) as well as RCTs with a placebo control group. The primary outcome was any

Figure 1. PRISMA Flow Diagram



NICE indicates UK National Institute for Health and Care Excellence; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

VTE event (including DVT and/or PE) after surgery, regardless of whether the event was asymptomatic or symptomatic. Secondary outcomes, where reported, included mortality, major bleeding complications (including gastrointestinal tract and cerebrovascular hemorrhage), other bleeding complications, and wound complications (eg, hematoma and infection). No limits were placed on study follow-up duration.

Data Extraction and Quality Assessment

The data extraction was conducted by 2 of us (G.S.M. and S.K.K) independently. In cases of inconsistency, consensus was reached by a third author (M.R.W.). A standardized predesigned data extraction form was used to obtain the relevant data from each study, including design, baseline demographic characteristics, geographical location, numbers enrolled and randomized, allocation concealment, blinding, VTE prophylaxis regimens (including dosage and duration), outcomes of interest, and follow-up duration. In cases of multiple publications involving the same study, the most up-to-date or comprehensive information was extracted.

Potential sources of bias in RCTs were assessed using the Cochrane Collaboration's risk of bias tool,[12] which assesses the following 7 possible sources of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. For each individual domain, studies were classified as having low, unclear, or high risk of bias.

Statistical Analysis

Summary measures are presented as relative risks (RRs) with 95% CIs. We used reported RRs, or we calculated risk estimates for studies that reported raw counts. Heterogeneity was assessed using the Cochrane χ^2 statistic and the I^2 statistic. Random-effects models, which take into account heterogeneity within and between studies, were used to combine RRs. Parallel analyses used fixed-effects models. The decision to use random-effects or fixed-effects models was based on I^2 quantification of heterogeneity, as well as variability in the clinical and methodological aspects of the studies, number of studies available for pooling, and study sample sizes.[13,14] Study-level characteristics—including geographical location, RCT design, allocation concealment, joint type (THR vs TKR), specific thromboprophylactic agent, VTE end point (DVT vs PE), and number of reported VTE events—were prespecified as characteristics for assessment of heterogeneity, which was conducted using stratified analysis and random-effects metaregression. Other characteristics explored post hoc included year of publication, follow-up duration, modern VTE diagnostic methods, type of VTE (symptomatic vs asymptomatic), use of mechanical VTE prophylaxis, and types and doses of anticoagulants reflecting modern practice. Potential for publication bias was assessed through formal tests (Begg funnel plots and Egger regression symmetry tests).[15] We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the quality of the body of evidence based on study limitations, inconsistency of effectiveness, imprecision, indirectness, and publication bias.[16] A statistical software program (Stata, version 14.2; StataCorp LLC) was used for all analyses. The level of statistical significance was set as $P < .05$, with 95% CIs also used. All statistical tests performed were 2 sided. Our study protocol was registered on PROSPERO (CRD42018118816).

Results

Study Identification

The initial search identified 437 potentially relevant citations (**Figure 1**). After screening titles and abstracts, 15 articles remained for full-text assessment. Two were subsequently excluded. Thirteen RCTs[9,11,17-27] (summarized in **Table 1** and **Table 2**) met the meta-analysis inclusion criteria.

Study Characteristics

The 13 RCTs[9,11,17-27] included 6060 participants (2969 aspirin and 3091 comparator), 3466 of whom (57.2%) were women. The mean age of participants was 63.0 years. Eleven trials[17-27] were open-label, and 2 trials[9,11] were double-blinded. Seven studies[9,11,18,22-25] were from North America, 4 studies[17,19,21,26] were from Asia, and 2 studies[20,27] were from Europe. Participant age ranged from 21 to 86 years. Seven studies[11,18,20,21,23,25,27] reported only on patients undergoing THR, 3 studies[9,17,22] reported on both patients undergoing THR and patients undergoing TKR, and 3 studies[19,24,26] reported only on patients undergoing TKR. The most common comparators were LMWH (5 studies[11,17,20,24,26]) or rivaroxaban (3 studies,[9,19,26] one of which used an initial 5-day course of LMWH followed by 14 days of rivaroxaban[19]). All studies[9,11,17-27] reported VTE events. Eleven studies[9,11,17,19-26] reported specifically on DVT, and 9 studies[9,11,17,18,20,22-25] reported specifically on PE.

Risk of Bias

Using the Cochrane Collaboration's risk of bias tool,[12] a total of 11 trials[17-27] had a high risk of bias, with each study having between 1 and 4 of the 7 possible sources of bias (eFigure 1 in

the Supplement). Bias was most common in blinding of participants and personnel followed by blinding of outcome assessment and allocation concealment. Two studies[9,11] had a low risk of bias in all domains.

Primary VTE Outcomes

In the whole cohort, the pooled risk of VTE after THR and TKR in patients receiving aspirin was not statistically significantly different from the risk in patients receiving other anticoagulants (RR, 1.12; 95% CI, 0.78-1.62) (**Figure 2**). There was evidence of heterogeneity between the included studies (I^2 = 63%; 95% CI, 33%-80%; P = .001), which was not explained by any of the study-level characteristics evaluated (**Figure 3**). On exclusion of the largest trial contributing data to the analysis (based on a noninferiority study design),[9] the pooled RR remained the same (1.14; 95% CI, 0.77-1.70), with minimal change in heterogeneity (I^2 = 66%; 95% CI, 38%-82%; P = .001). The pooled risk of DVT (11 studies[9,11,17,19-26]) (RR, 1.04; 95% CI, 0.72-1.51) and PE (9 studies[9,11,17,18,20,22-25]) (RR, 1.01; 95% CI, 0.68-1.48) after THR and TKR in patients receiving aspirin also were not statistically significantly different compared with patients receiving other anticoagulants.

Adverse Events

There was variable reporting of adverse events among the studies. The most common adverse event reported was wound hematoma (5 studies[20,21,23,25,27]) followed by major bleeding (3 studies[9,11,23]), wound infection (3 studies[9,11,23]), and other wound complications (3 studies[19,22,26]). In the pooled analysis, the risks of the following events were not statistically significantly different in patients receiving aspirin vs other anticoagulants: any bleeding, major bleeding, minor bleeding, gastrointestinal tract bleeding, wound hematoma, wound infection, other wound complications, myocardial infarction, and death (eFigure 2 in the Supplement). Patients receiving aspirin had a statistically significantly reduced pooled risk of bruising (RR, 0.68; 95% CI, 0.54-0.84) and lower limb edema (RR, 0.57; 95% CI, 0.37-0.88) compared with those receiving comparators.

Subgroup Analysis

Because of limited data, subgroup analysis only assessed the primary outcome of interest (VTE). There was no evidence of effect modification by any of the clinically relevant study-level characteristics explored (Figure 3). Specifically, the type of joint surgery (THR vs TKR) and thromboprophylactic agent did not alter the risk of VTE. In the 5 studies[11,17,20,24,26] reporting on VTE in patients receiving LMWH, the risk of VTE was not statistically significantly different in patients receiving aspirin vs LMWH (RR, 0.76; 95% CI, 0.37-1.56). The risks of DVT (RR, 0.83; 95% CI, 0.42-1.63) and PE (RR, 0.71; 95% CI, 0.19-2.61) were also not statistically significantly different. In the 3 studies[9,19,26] reporting on VTE events in patients receiving aspirin compared with rivaroxaban (with or without an initial course of LMWH), the risks of VTE (RR, 1.52; 95% CI, 0.56-4.12) and DVT (RR, 1.67; 95% CI, 0.53-5.26) were also not statistically significantly different. Further subgroup analyses by study-level characteristics, such as year of publication, follow-up duration, modern VTE diagnostic methods, type of VTE, types and dosages of anticoagulants reflecting modern practice, and equal distribution of mechanical VTE prophylaxis, did not demonstrate any evidence of effect modification.

Table 1. Summary Characteristics of the Included 13 Randomized Clinical Trials[9,11,17-27]

Characteristic	Value
No. of participants	
Total	6060
Aspirin	2969
Comparator[a]	3091
Age, mean (range), y	63 (21-86)
Female, No. (%)	3466 (57.2)
Joint replacement population	
Both THR and TKR	3 Studies[9,17,22] (n = 3857)
THR only	7 Studies[11,18,20,21,23,25,27] (n = 1495)
TKR only	3 Studies[19,24,26] (n = 708)
Geographical location	
North America	7 Studies[9,11,18,22-25] (n = 5223)
Asia	4 Studies[17,19,21,26] (n = 665)
Europe	2 Studies[20,27] (n = 172)
Comparator[a]	
Rivaroxaban with or without LMWH	3 Studies[9,19,26] (n = 1879)
LMWH	5 Studies[11,17,20,24,26] (n = 747)
Warfarin sodium	3 Studies[22,23,25] (n = 258)
LMW dextran	4 Studies[18,21,23,27] (n = 173)
Dipyridamole	1 Study[23] (n = 34)
Outcome[b]	
VTE	13 Studies[9,11,17-27] (n = 6060)
DVT	11 Studies[9,11,17,19-26] (n = 5835)
PE	9 Studies[9,11,17,18,20,22-25] (n = 5426)
Follow-up duration for outcome assessment, range (when specified)	9 d to 6 mo

Abbreviations: DVT, deep vein thrombosis; LMW, low-molecular-weight; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism.

[a] Studies could report on more than 1 comparator vs aspirin. Two studies[23,26] reported on more than 1 comparator vs aspirin (see Table 2 for details).

[b] Studies could report on more than 1 outcome. All but 2 studies[21,27] reported on 2 or more outcomes from VTE, DVT, and PE.

Publication Bias

For comparisons involving 10 or more studies, visual inspection of Begg funnel plots for studies of VTE and DVT were symmetrical (eFigure 3 in the Supplement). These were also consistent with Egger regression symmetry tests, demonstrating no statistically significant evidence of publication bias.

GRADE Ratings

GRADE ratings for outcomes involving pooled analyses of 5 or more studies were assessed (eTable 2 in the Supplement). The quality of evidence for VTE, DVT, PE, and wound hematoma ranged from low to high.

Table 2. Specific Details of the Treatment Arms and Outcomes for the Included 13 Randomized Clinical Trials[9,11,17-27]

Source	No. of Participants	Dosage and Duration		Use of Mechanical VTE Prophylaxis	Routine DVT Screening or Symptomatic DVT	DVT Diagnostic Methods	Follow-up Duration
		Aspirin	Comparator				
Anderson et al,[9] 2018	THR: 1804 TKR: 1620	5 d Rivaroxaban (10 mg once daily) then aspirin (81 mg once daily) for 30 d for THR, and 9 d for TKR	Rivaroxaban (10 mg once daily) for 35 d for THR, and 14 d for TKR	As per local policy (none, IPC, graduated stockings, or both) (equal distribution of these between treatment groups)	Symptomatic	Venous ultrasonography	90 d
Jiang et al,[19] 2014	TKR: 120	14 d Aspirin (100 mg once daily)	5 d LMWH (5000 U once daily) then 14 d of rivaroxaban (10 mg once daily)	IPC plus graduated stockings in both groups	Routine screening (fourth and fifth postoperative days) plus any symptomatic VTE during follow-up	Venous ultrasonography	6 wk
Zou et al,[26] 2014	TKR: 324	14 d Aspirin (100 mg once daily)	14 d of Rivaroxaban (10 mg once daily) or 14 d of LMWH (4000 U once daily)	NS	Routine screening (second and fourth postoperative weeks) plus any symptomatic VTE during follow-up	Venous ultrasonography	4 wk
Anderson et al,[11] 2013	THR: 778	10 d of LWMH (dalteparin sodium 5000 U once daily) then aspirin (81 mg once daily) for 28 d	38 d LWMH (dalteparin sodium 5000 U once daily)	As per local policy (NS what used or how distributed between groups)	Symptomatic	Venous ultrasonography	90 d
Westrich et al,[24] 2006	TKR: 264	28 d Aspirin (325 mg once daily)	28 d LWMH (enoxaparin sodium 40 mg once daily)	IPC in both groups	Routine screening (3-5 d after surgery, and 4-6 wk after surgery) plus any symptomatic VTE during follow-up	Venous ultrasonography	6 wk
Gelfer et al,[17] 2006	THR and TKR: 121	Aspirin (100 mg once daily; duration NS)	LWMH (enoxaparin sodium 40 mg once daily; duration NS)	IPC in aspirin group only	Routine screening (5-8 d after surgery) plus any symptomatic VTE during follow-up	Venogram for screening plus venous ultrasonography for symptomatic events	3 mo
Kim et al,[21] 1998	THR: 100	16 d Aspirin (1200 mg once daily)	3 d LMW dextran (500 mL once daily)	NS	Routine screening (7-10 d after surgery)	Venogram	10 d
Woolson and Watt,[25] 1991	THR: 141	Aspirin (650 mg twice daily; duration NS)	Warfarin sodium (7.5 mg or 10 mg initially then dose titrated based on prothrombin time; duration NS)	IPC plus graduated stockings in both groups	Routine screening (4-13 d after surgery) plus any symptomatic VTE during follow-up	Venogram and/or venous ultrasonography	3 mo
Josefsson et al,[20] 1987	THR: 82	9 d Aspirin (1500 mg twice daily)	9 d Dihydroergotamine mesylate-heparin sodium (dihydroergotamine mesylate 0.5 mg-heparin sodium 5000 U twice daily)	Graduated stockings in both groups	Routine screening (9 d after surgery)	Lung perfusion scan and fibrinogen uptake test (venogram done if uptake scan was positive)	9 d
Harris et al,[18] 1985	THR: 135	Aspirin (1200 mg once daily; duration NS) or aspirin (300 mg once daily; duration NS)	3 d LMW dextran (once daily; dose NS)	IPC in LMW dextran group only	Routine screening (see cell to the right for timings) plus any symptomatic VTE during follow-up	Fibrinogen uptake test (daily), cuff impedance (4-5 d after surgery then every third day), and venography (done before postoperative d 10 if one of above was positive, otherwise done between postoperative d 10 and 14)	14 d
Lotke et al,[22] 1996	THR: 133 TKR: 179	42 d Aspirin (325 mg twice daily)	42 d Warfarin sodium (10 mg initially then dose titrated based on prothrombin time)	NS	Routine screening (7-10 d after surgery) plus any symptomatic VTE during follow-up	Lung perfusion scan and venogram	6 mo

(continued)

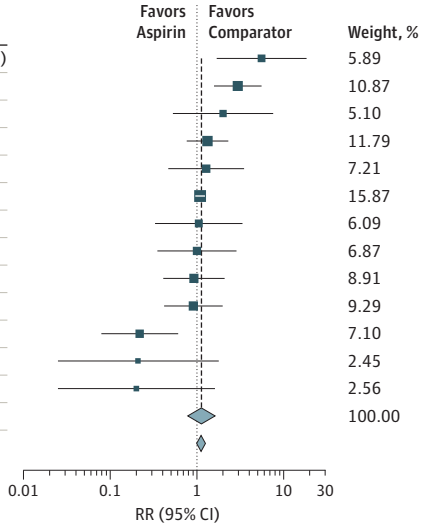
Table 2. Specific Details of the Treatment Arms and Outcomes for the Included 13 Randomized Clinical Trials[9,11,17-27] (continued)

Source	No. of Participants	Dosage and Duration		Use of Mechanical VTE Prophylaxis	Routine DVT Screening or Symptomatic DVT	DVT Diagnostic Methods	Follow-up Duration
		Aspirin	Comparator				
Salzman et al,[23] 1971	THR: 169	21 to 35 d Aspirin (600 mg twice daily)	21-35 d of Warfarin sodium (dose titrated based on prothrombin time),or dipyridamole (400 mg once daily), or dextran (500 mL/10% solution once daily)	NS	Symptomatic	Lung perfusion scan and pulmonary angiography (no venogram or fibrinogen uptake test used for DVT detection)	NS
Alfaro et al,[27] 1986	THR: 120	7 d Aspirin (125 mg twice daily) or 7 d aspirin (500 mg twice daily)	7 d Dihydroergotamine mesylate-heparin sodium (dihydroergotamine mesylate 0.5 mg-heparin sodium 5000 U twice daily)	NS	Routine screening (minimum of 7 d after surgery)	Fibrinogen uptake test (venogram done if uptake scan was positive)	NS

Abbreviations: DVT, deep vein thrombosis; IPC, intermittent pneumatic compression; LMW, low-molecular-weight; LMWH, low-molecular-weight heparin; NS, not specified; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism.

Figure 2. Effectiveness of Aspirin Compared With Other Anticoagulants on Venous Thromboembolism (Including Deep Vein Thrombosis and Pulmonary Embolism) in Randomized Clinical Trials of Patients Undergoing Total Hip and Knee Replacement

Source	Aspirin		Comparator		RR (95% CI)	Weight, %
	No. of Events	No. of Participants	No. of Events	No. of Participants		
Zou et al,[26] 2014	18	110	3	102	5.56 (1.69-18.33)	5.89
Harris et al,[18] 1985	26	43	9	44	2.96 (1.57-5.55)	10.87
Kim et al,[21] 1998	6	50	3	50	2.00 (0.53-7.56)	5.10
Westrich et al,[24] 2006	24	129	19	135	1.32 (0.76-2.29)	11.79
Woolson et al,[25] 1991	8	72	6	69	1.28 (0.47-3.49)	7.21
Lotke et al,[22] 1996	131	166	106	146	1.09 (0.96-1.23)	15.87
Josefsson et al,[20] 1987	5	40	5	42	1.05 (0.33-3.35)	6.09
Salzman et al,[23] 1971	6	43	6	43	1.00 (0.35-2.86)	6.87
Anderson et al,[9] 2018	11	1707	12	1717	0.92 (0.41-2.08)	8.91
Jiang et al,[19] 2014	10	60	11	60	0.91 (0.42-1.98)	9.29
Gelfer et al,[17] 2006	4	61	18	60	0.22 (0.08-0.61)	7.10
Anderson et al,[11] 2013	1	380	5	398	0.21 (0.02- 1.78)	2.45
Alfaro et al,[27] 1986	1	30	5	30	0.20 (0.02-1.61)	2.56
Random effects					1.12 (0.78-1.62)	100.00
Fixed effects					1.11 (0.99-1.25)	



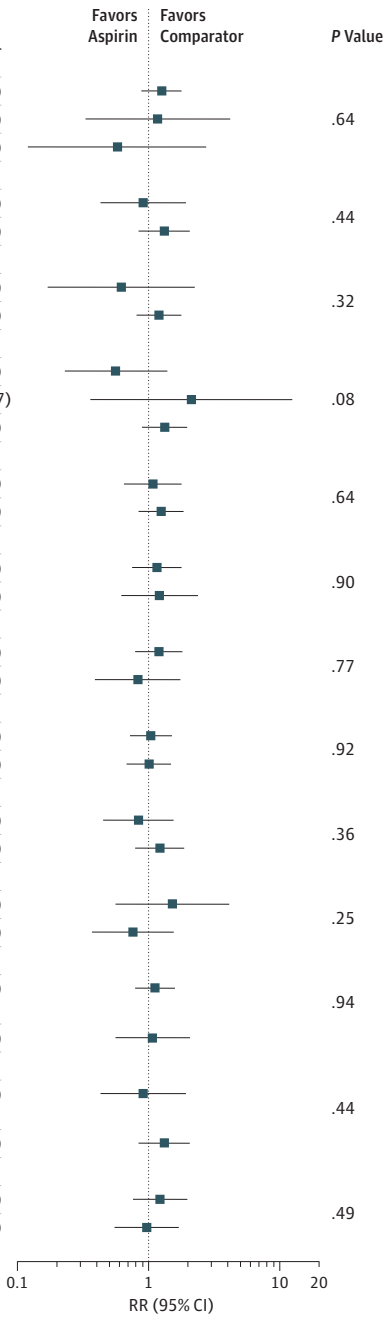
Thirteen randomized clinical trials[9,11,17-27] were included. Outcomes included both symptomatic and asymptomatic venous thromboembolism events. The summary estimate presented was calculated using a random-effects model. Sizes of data markers are proportional to the inverse of the variance of the relative ratio. RR indicates relative risk. The diamonds represent the overall estimated relative risk (with 95% CIs) for the 13 trials combined when using a random-effects model and when using a fixed-effects model.

Discussion

This systematic review and meta-analysis of RCTs demonstrated that there was no statistically significant difference in the risk of VTE (including DVT and PE) when comparing aspirin with other anticoagulants for VTE prophylaxis in patients undergoing THR and TKR. The findings for VTE remained consistent when patients undergoing THR and TKR were assessed separately as well as when comparing aspirin with other commonly used anticoagulants, including LMWH and rivaroxaban. There were no differences in the risk of adverse events, such as bleeding, wound complications, myocardial infarction, and death, when aspirin was compared with other anticoagulants, although patients receiving aspirin had a reduced risk of bruising and lower-limb edema. Findings for adverse events were based on data reported by few studies, and some of the estimates were imprecise; therefore, caution is needed when interpreting these results. In addition, RCTs were heterogeneous in terms of populations studied (THR and/or TKR) and anticoagulants compared with aspirin (specific drug and dosage). However, formal subgroup analyses confirmed that the main study findings were not modified by study-level characteristics, including geographical location, RCT design, allocation concealment, type of surgery (THR vs TKR), specific thromboprophylactic agent, VTE end point (DVT vs PE), number of

Figure 3. Effectiveness of Aspirin Compared With Other Anticoagulants on Venous Thromboembolism (VTE) in Randomized Clinical Trials of Patients Undergoing Total Hip and Knee Replacement, Grouped According to Study-Level Characteristics

Subgroup	No. of Studies	Aspirin No. of Events	Aspirin No. of Participants	Comparator No. of Events	Comparator No. of Participants	RR (95% CI)	P Value
Location							
North America[9,11,18,22-25]	7	207	2540	163	2552	1.26 (0.88-1.79)	.64
Asia[17,19,21,26]	4	38	281	35	272	1.17 (0.33-4.20)	
Europe[20,27]	2	6	0	10	72	0.58 (0.12-2.75)	
Year of publication							
After 2000[9,11,17,19,24,26]	6	68	2447	68	2472	0.91 (0.43-1.93)	.44
Before 2000[18,20-23,25,27]	7	183	444	140	424	1.32 (0.84-2.06)	
RCT design							
Double-blind[9,11]	2	12	2087	17	2115	0.62 (0.17-2.25)	.32
Open label[17-27]	11	239	804	191	781	1.20 (0.81-1.78)	
Allocation concealment							
Adequate[9,11,17,25]	4	24	2220	41	2244	0.56 (0.23-1.39)	.08
Unclear[19,26,27]	3	28	170	14	162	2.12 (0.36-12.47)	
Inadequate[18,20-24]	6	199	501	153	490	1.33 (0.89-1.97)	
Joint type							
THR[9,11,17,18,20-23,25,27]	10	75	1622	70	1649	1.08 (0.65-1.79)	.64
TKR[9,17,19,22,24,26]	6	135	1208	92	1187	1.25 (0.84-1.85)	
Follow-up duration, d							
≥14[9,11,17-19,21,22,24-26]	10	233	2728	189	2731	1.16 (0.75-1.79)	.90
<14[20,23,27]	3	17	133	14	135	1.21 (0.62-2.38)	
Modern VTE diagnosis							
Yes[9,11,17-19,21,22,24-26]	10	239	2778	192	2781	1.20 (0.79-1.81)	.77
No[20,23,27]	3	12	113	16	115	0.83 (0.39-1.75)	
VTE end point							
DVT[9,11,17,19-26]	11	181	2848	155	2852	1.04 (0.72-1.51)	.92
PE[9, 11,17,18,20,22-25]	9	46	2641	43	2654	1.01 (0.68-1.48)	
Type of VTE							
Symptomatic[9,11,23]	3	18	2130	23	2158	0.84 (0.45-1.55)	.36
Asymptomatic[17-22,24-27]	10	233	761	185	738	1.22 (0.79-1.87)	
Regimen comparison							
Aspirin vs rivaroxaban[9,19,26]	3	39	1877	26	1978	1.52 (0.56-4.12)	.25
Aspirin vs LMWH[11,17,20,24,26]	5	52	720	61	747	0.76 (0.37-1.56)	
Mechanical VTE prophylaxis							
Distributed equally between groups[9,18-20,24,25]	6	58	2008	53	2023	1.12 (0.79-1.59)	.94
None[11,17,21-23,26, 27]	7	193	883	155	873	1.07 (0.56-2.07)	
Type/doses of anticoagulants							
Reflecting modern practice[9,11,17,19,24,26]	6	68	2447	68	2472	0.91 (0.43-1.93)	.44
Others[18,20-23,25,27]	7	183	444	140	424	1.32 (0.84-2.06)	
No. of VTE events							
≥20[9,17-19,22,24,26]	7	224	2276	178	2264	1.22 (0.76-1.98)	.49
<20[11,20,21,23,25,27]	6	27	615	30	632	0.97 (0.55-1.70)	



Thirteen randomized clinical trials[9,11,17-27] were included. Outcomes included both symptomatic and asymptomatic VTE events. *P* values are for meta-regression. DVT indicates deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; RCT, randomized clinical trial; RR, relative risk; THR, total hip replacement; and TKR, total knee replacement.

reported VTE events, publication year, type of VTE (symptomatic vs asymptomatic), types and doses of anticoagulants reflecting modern practice, modern VTE diagnostic methods, use of mechanical VTE prophylaxis, and follow-up period. The quality of the evidence ranged from low quality to high quality for the primary outcomes of VTE and/or DVT and PE and for the most commonly reported complication of wound hematoma.

Our findings are consistent with large observational cohorts,[4,5,28-31] which have reported that aspirin was effective for VTE prophylaxis and that aspirin had a similar or slightly improved effectiveness and safety profile compared with other commonly used anticoagulants. Therefore, we believe current evidence supports the continued use of aspirin in VTE prophylaxis after THR and TKR.

The inclusion of a recent RCT[9] in this meta-analysis was important given that it was large, represented one of only 2 studies[9,11] appraised that had a low risk of bias,[9] and was one of only a few studies[9,19,26] comparing the newer oral anticoagulants (eg, rivaroxaban) with aspirin, albeit after an initial 5-day course of rivaroxaban for all patients. Furthermore, this RCT[9] has not been considered in any previous evidence synthesis to date and thus could change the interpretation of existing data. The authors of the trial observed no difference in the risk of VTE or adverse events between aspirin and rivaroxaban. That single trial comprised more than half of the patients included in our systematic review and meta-analysis. However, analyses excluding that large trial also demonstrated that aspirin was not statistically significantly different from LMWH, which is an alternative current method of VTE prophylaxis frequently used worldwide.

We consider the current evidence on VTE prophylaxis after THR and TKR to be more in line with the recommendations from the ACCP[7] rather than the NICE,[8] with the latter still not recommending aspirin monotherapy after THR, despite supportive evidence provided herein and from other studies.[5,29] However, given that most current trials[17-27] included in our study had a high risk of bias, we still require robust data from large well-designed RCTs to explore the efficacy, safety, and cost-effectiveness of aspirin compared with other commonly used anticoagulants. A current RCT in North America will randomize 25 000 patients undergoing THR and TKR either to aspirin, warfarin sodium, or rivaroxaban to determine the efficacy and safety of each drug for VTE prophylaxis[32]; however, that study does not include commonly used anticoagulant agents, such as dabigatran and LMWH. It is acknowledged that some VTE prophylactic agents are becoming less popular in certain regions or countries because of potential drawbacks compared with aspirin and direct oral anticoagulants. For example, LMWH requires daily injections administered by either the patient or health care professionals, and warfarin requires regular blood testing to ensure therapeutic levels of anticoagulation, with potentially life-threatening consequences if patients are excessively anticoagulated.

Strengths and Limitations

This study has several strengths. The present systematic review and meta-analysis is the first to include the largest RCT[9] to date in this area, thus providing the most comprehensive update on the effectiveness and safety of aspirin for VTE prophylaxis after THR and TKR. We have used a detailed and robust search strategy that spanned multiple databases and was without language restriction. This allowed us to include trials from all over the world, improving the generalizability of our findings. Only RCTs were included; therefore, by excluding observational studies, we removed the inherent selection bias associated with this study design. A detailed assessment of methodological quality of the included studies was performed. We systematically explored for sources of heterogeneity using several study-level characteristics and tested for evidence of effect modification. Notably, we stratified our analyses for patients undergoing THR and TKR and compared aspirin with specific anticoagulants, which have been limitations of previous trials and systematic reviews. Our results remained robust in several sensitivity analyses, and formal testing demonstrated no evidence of publication bias.

There were several limitations, with most inherent to the meta-analysis. The analysis was limited by the few relevant RCTs[9,11,17-27] that have been published and small sample sizes given the outcomes of interest. The low adverse event rate in some trials led to wide 95% CIs around the RRs, thus reducing the precision of the respective estimates. Most studies[17-27] had a high risk of bias in at least 1 domain. Furthermore, there was variability in the populations assessed (THR, TKR, or both), aspirin dosage and duration, the comparator (drug, dosage, and duration), the reporting of outcomes (including routine VTE screening vs symptomatic VTE) and adverse events, use of mechanical VTE prophylaxis, and follow-up duration. These factors potentially could have led to biased estimates, despite being assessed in sensitivity analyses. There appeared to be selective reporting on adverse events because these data were not reported by some of the included studies, which could have led to loss of power to demonstrate if any associations existed. There was statistically significant heterogeneity among the studies[9,11,17-27] that could not be explained by several relevant study-level characteristics, suggesting that other factors might be responsible. It is acknowledged that there is bias toward overreporting symptomatic DVT in the trials[17-22,24-27] that routinely screened for asymptomatic DVT given that the latter is frequently treated when identified. In addition, a large RCT[9] contributed more than 50% of the overall sample size; however, exclusion of this study in sensitivity analysis did not change the overall results.

Conclusions

Available evidence from RCTs suggests that in terms of clinical effectiveness and safety, aspirin is not statistically significantly different from other anticoagulants used for VTE prophylaxis after THR and TKR. The body of evidence ranges from low quality to high quality. However, given that most of the relevant current trial evidence has a high risk of bias, additional large, well-designed RCTs are needed to validate these findings. Furthermore, these trials must determine whether newer, more expensive anticoagulants (including rivaroxaban and dabigatran) have any clinical benefit over aspirin for VTE prophylaxis after THR and TKR and whether these drugs are cost-effective.

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